UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

JOHN DOE #1 et al.	*	
	*	
Plaintiffs,	*	
	*	Civil Action No.: 1:03CV00707 (EGS)
v.	*	
	*	
DONALD H. RUMSFELD et al.,	*	
	*	
Defendants.	*	

* * * * * * * * * * * * *

DECLARATION OF SAMMIE R. YOUNG

I, SAMMIE R. YOUNG, pursuant to 28 U.S.C. § 1746, hereby declares as follows:

1. I am a person over eighteen (18) years of age and competent to testify. I make this Declaration on personal knowledge and in further support of the Plaintiffs' Response to the Court Order of May 26, 2004.

Background

2. I am Sammie R.Young (Colonel, USAFR, (MSC) ret.) and I served from 1963-1992 as a regulatory compliance officer of the Food and Drug Administration (FDA), where I had direct knowledge of, and responsibility for, the regulatory issues before the Court in Doe v. Rumsfeld. I have reviewed Defendants' filings in this case, as well as the three declarations[1] filed on behalf of Defendants in this case, and the Administrative Record submitted by FDA in support of its Final Rule.[2]

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[1] By FDA Dr. Jesse Goodman, Ph.D., director of FDA's Center for Biologic Evaluation and Research; US Army Colonel John Grabenstein, Ph.D.; and Dr. William Winkenwerder, M.D.

[2] I have closely followed the anthrax vaccine debate since contacting the military officer who authored a *Washington Post* Outlook section op-ed published in 2000. ("Sticking Point: Why Am I Resisting the Vaccine? The Military Trained Me To", by Tom Rempfer, *Washington Post*, Jan 30, 2000; Page B01). I have previously submitted a declaration in another anthrax vaccine lawsuit (Barber v. Caldera, Civil Action 00-N-1022, U.S. Dist. Ct. for Colorado). I also participated in an NIH conference held on Dec. 15, 2001 to discuss

Civilian background

3. I graduated from the University of Florida in 1951, with a Bachelor of Science in biology, entered the military for 11 years of active duty service (see below), and in 1963, I joined the FDA. From 1975-1992, I was primarily involved in compliance, including the regulation and approval of human drugs, and the licensing of biologics (vaccines, blood and blood products). During my career as a regulator I regularly participated in in-house training programs on regulatory law, writing regulations, and drafting Federal Register announcements relating to regulatory policy. Additionally, I took a regulatory law course at George Washington University taught by former FDA General Counsel William Goodrich. I retired from FDA in 1992.[3]

4. From 1975-1983 I served as the Director, Division of Compliance, at FDA's Bureau of Biologics[4] where I was responsible for a nationwide inspection and sampling program; the development of facts required to support legal actions directed at manufacturers of biologics and blood products found to be in violation of the federal Food Drug and Cosmetic Act ("FD&C Act") and the Public Health Service Act (PHSA); and the

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post-exposure prophylaxis with AVA. See NIH transcript at pages 123-125: *www.bt.cdc.gov/DocumentsApp/Anthrax/12172001/1215HHSTranscript.pdf*.

[3] While at the FDA, I received numerous awards and commendations, including the FDA Award of Merit (the agency's highest award) in 1990, and a special letter of commendation in 1992. On December 4, 1992 the *Washington Post* reported on my retirement from FDA after 40 years of federal service. On February 16, 1993 the *Congressional Record* contained a tribute honoring my retirement, which noted "that Mr. Young was instrumental in the development and implementation of the surveillance and compliance programs for all biological products, including blood, blood products and vaccines regulated by FDA Bureau of Biologics." (See Attachment "A"). Finally, on April 19, 1997, the Maryland state senate passed a resolution honoring me for my career of dedicated public service.

[4] This was the predecessor of the FDA's current Center for Biologics Evaluation and Research (CBER) division, the agency that has had oversight of both AVA's product license and the manufacturer's facility license.

development of compliance and surveillance programs and standards (including regulations) covering the biologics industry. In this capacity I provided expert opinion on regulatory issues to the FDA expert review panel that reviewed numerous biologic products, including the anthrax vaccine absorbed ("AVA"), from 1973-1979. (See FDA Administrative Record ("AR") at 16).

5. From 1983-1992, I served as the Deputy Director of the Office of Compliance at the Center for Drug Evaluation and Research (CDER). As Deputy Director I shared responsibility for managing and directing a multidisciplinary staff engaged in planning, executing, and administering the FDA's regulatory program related to drugs, including:

- The development of agency strategy in the areas of drug quality, manufacturer quality assurance, product surveillance, certification and bioresearch monitoring;
- The evaluation of field reports, including inspections, investigations, and recommendations for compliance actions;
- The direction and coordination of case development and contested-case assistance to FDA attorneys in the handling of compliance actions;
- The development of guidelines and standards for new drugs, including current Good Manufacturing Practices (cGMP) for drug manufacturing; and,
- The development of regulations and agency documents published in the Federal Register relating to the agency's regulatory programs.

Military background

6. I am a retired U.S. Air Force Reserve Medical Service Corps colonel. I served in the Air Force for 28 years, including 11 years of active duty in operational flying assignments and 17 years as an Air Force Reserve Medical Service Corps (MSC) officer.

While in the Air Force, I served in healthcare positions as a Clinical Laboratory Officer and as a Health Service Hospital Administrator.

Purpose

7. In this declaration I will discuss the origins of FDA's regulation of biologics, including AVA; the regulatory intent of FDA administrative rulemaking, including 21 CFR 601.25; and explain how FDA's regulatory actions relating to AVA, including its 2004 Final Rule, deviate from well-established agency policy and past practice.

1. FDA's licensing authority over biologic products.

8. The case before the Court goes to the exact reasons why FDA was given regulatory authority over biologics in 1972, and why the law grants this court jurisdiction over issues raised in Doe v. Rumsfeld. Understanding the historical context[5] of this redelegation from the National Institutes of Health (NIH) Division of Biologics Standards (DBS) to FDA is crucial to the Court understanding the rationale for the FDA's 1973-1979 review of all licensed biologics.

9. In 1962, Congress passed the Harris-Kefauver Act[6], an amendment to the FD&C Act passed in direct response to FDA having allowed the use of thalidomide on pregnant women and the severe birth defects that resulted. This amendment included three

[5] On February 21, 1980 FDA accepted a Citizen Petition (docket 80P-0067/CP) (See Attachment "B") from the Public Citizen Health Research Group (hereinafter, "HRG") that was filed in response to the August 2, 1979 recommendations (AR 26) of the FDA expert panel that reviewed AVA and other biologics. This Citizen Petition (HRG at p. 2-8) thoroughly and accurately recounts the statutory record leading to FDA's regulation of biologics. For brevity it is not recounted here. For additional historical context, see also FDA's Proposed Rule and Final Rule promulgated in response to the HRG Citizen Petition: 46 Fed. Reg. 4634 et. seq. (Jan 16, 1981); and, 47 Fed. Reg. 44062 et. seq. (Oct. 5, 1982), respectively. The latter is a detailed expression for the FDA's intent with respect to implementation of 21 CFR 60.25.

[6] Public Law 87-261, Drug Industry Act of 1962.

fundamental changes to the FD&C Act: (a) a requirement that there must be "substantial evidence" that drugs and vaccines are safe and effective to be approved or licensed; (b) a requirement that FDA include a risk-benefit analysis in its licensure decisions; and, (c) a requirement that manufacturers comply with established quality control standards, termed current Good Manufacturing Practices (cGMP). When I entered the FDA the following year, the agency was already heavily engaged in a decade long effort, the Drug Efficacy Study Implementation (DESI), to review all drugs to insure they met the new requirements of the FD&C Act. The DESI review ultimately culminated in Supreme Court cases in 1972-1973 that upheld FDA's authority to remove drugs from the market when their manufacturers could not demonstrate safety or efficacy.[7] The Supreme Court upheld FDA because it recognized that the DESI review, and the regulatory decisions that followed from it, were the result of a ***statutory mandate*** from Congress – not a voluntary undertaking by FDA.

10. Unfortunately, and contrary to this statutory mandate, no similar DESI-like review of vaccines was initiated by the National Institutes of Health (NIH) Division of Biologic Standards (DBS) for over a decade after the passage of the 1962 Harris-Kefauver Act. For reasons well-explained in the 1980 HRG Citizen Petition, and earlier acknowledged by FDA (See 37 Fed. Reg. 16679, Aug. 18, 1972) when it assumed regulation of vaccines, all licensed vaccines should have been required to prove safety and efficacy in accordance with the standards of the FD&C Act after it was amended in 1962. However, DBS's leadership insisted that their agency was only required to enforce the PHSA requirements for 'safety, purity and potency', and that DBS lacked the legal authority to enforce the

[7] See e.g., Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, (1973).

FD&C Act requirement for efficacy.[8] In response, on May 25, 1972, Health Education and Welfare Secretary Elliott Richardson announced that DBS would be transferred from NIH to FDA.

11. FDA subsequently implemented a review process in the 1970's that made slow, steady progress in bring most biologic products into compliance with the Harris-Kefauver provisions of the FD&C Act.

2. FDA's expert review panel's expertise.

12. FDA's decision to contradict its 1985 expert review panel's efficacy findings in its Final Rule (See 69 Fed. Reg. 259-260, Jan. 5, 2004), in the absence of any evidence that the panel was denied any relevant information during its deliberations, is troubling. The expert panel that reviewed vaccines, including AVA, met for six years (1973-1979). During that time NIH's Dr. Margaret Pittman, a legendary vaccine researcher[9], served as the sole consultant to the FDA expert review panel (See Administrative Record (AR) 11). She had previously served as the chairman of the DBS ad hoc licensure committee for AVA. On Feb. 10, 1969, Dr. Pittman recommended licensure of AVA subject to CDC being "requested to obtain data with a view to determine human efficacy of the product," (See AR 4019), but there is no record of any such data ever being provided. Further, in 1973, the FDA expert review committee received a submission from the manufacturer, MDPH, that

[8] See GAO Report B-164031(2), "Problems Involving the Effectiveness of Vaccines," Mar. 28, 1972, p. 12-13, at Attachment "C".

[9] Dr. Pittman was later appointed to be NIH's first woman laboratory chief, the most prestigious scientist position at NIH.

made clear that AVA's efficacy in humans was not proven, and that the Brachman vaccine had only demonstrated efficacy for cutaneous anthrax. See AR 3290-3302.[10]

13. Additionally, Dr. Brachman was given the opportunity to appear before the FDA expert review panel and express his views on his study findings. See AR 11-12. Since the final report of the review panel was submitted in 1979 (See AR 26) and made publicly available a year later (See AR 1) (See also 45 Fed. Reg. 77134, Nov. 21, 1980), FDA regulatory personnel had over six years to correct any misunderstanding on the part of the expert review panel prior to publishing a Proposed Rule in 1985.

3. FDA's 1985 Proposed Rule and 2004 Final Rule, including the licensure of AVA, are administrative rulemaking.

14. FDA and DoD asserted that, "Indeed, it is hard to see how FDA's decision could be viewed as anything but an "order" for purposes of the APA." See Def. S.J. Opp., at 17, Apr. 7, 2004. This argument ignores the fact that FDA's well-established administrative practices have never fully mirrored the Administrative Procedures Act.

15. First, FDA employees have historically used the terms "Rule" and "Order" interchangeably. One needs only to look at Dr. Goodman's declaration (at 3-4) for an example: in paragraph 7 he used "orders"; in paragraph 9 he used "rule."[11] Further, Dr. Goodman specifically relates the word "rule" (and not "order") to FDA's formulation of a

[10] "Analysis by the Center for Disease Control of one field trial of an earlier lot of this antigen in man, occupationally at risk of contracting anthrax, *has indicated 92% effectiveness in prevention of cutaneous anthrax*. Because of the infrequency of human inhalation of [sic] anthrax, it is not possible at this time to provide a quantitative estimate of the efficacy of the MDPH vaccine in conferring protection in man against either form of the disease." (emphasis added).

[11] Another example of "Rule" and "Order" being used interchangeably, specific to FDA's Dec. 13, 1985 Proposed Rule for AVA, can be found at 65 Fed. Reg. 31003 et. seq. (May 15, 2000) at paragraph 2.

Rule for anthrax vaccine (and not the other ancillary issues addressed in the Rule): "While FDA has not yet finalized the proposed rule *relating to the anthrax vaccine*…"(emphasis added).

16. Second, within the context of FDA's historic practices, "Rules" and "Orders" have had the same practical effect: "administrative rule making." This process was explained in the Commissioner's 1977 response to comments on a Final Rule relating to "Administrative functions, practices, procedures." See 42 Fed. Reg. 4680-4696 (Jan 25, 1977). In explaining agency responses "relating to administrative matters subject to citizen petitions" (i.e., FDA's inaction in promulgating a Final Rule on AVA), the Commissioner clearly explained a non-litigious process intended to "promote conservation of judicial resources." Id. at 4688. In thus rejecting limitations on citizen petitions, the Commissioner made clear that the Proposed Rule and Final Rule relating to AVA are "rule making":

> The Commissioner does not accept these arguments, and…finds that those comments that attempt to characterize *administrative rule making* resulting from citizen petitions as a type of litigation, and those that equate requiring inclusion of "unfavorable information" with self-incrimination, misunderstand the nature of *administrative rule making*. In *rule making*, the agency is attempting to make judgments about regulatory policy on the basis of all of the scientific information that is available on a subject. There is thus no valid analogy between the interests of participants in a *rule making* proceeding and the interests of those involved in a criminal trial.

Id. at 4685.

17. In contrast, FDA's actions with respect to the licensure of AVA can only be seen as analogous to the actions of a criminal litigant for the simple reason that the agency has broken the law and its bureaucrats understand that it has done so.

4. FDA's Final Rule does not comply with established agency practices or statutory mandates.

a. FDA should have provided a new comment period prior to issuing a Final Rule on AVA.

18. FDA's 1972 guidance that led to the creation of 21 CFR 601.25 anticipated the expert review panel would consider "published and unpublished data and information pertinent to a designated category of biological product." See 37 Fed.Reg.16680 (Aug. 18, 1972). The dramatically expanded knowledge base related to DoD's use of AVA on over one million servicemembers since 1990, inherently means that whatever judgments the expert panel reached in 1979 had become overcome by the experience of the last 25 years since its report. This alone warranted a new comment period.

19. The Commissioner explicitly stated the agency's intent for this process in FDA's 1977 Final Rule on administrative practices that goes to the agency's once well-established regulatory "state of mind":

> The Commissioner disagrees with the comment's contention that any interested person should not be entitled to petition to modify or reverse any agency action, including one that may have initially been taken ex parte, such as approval of an NDA or NADA. The effects of such actions clearly extend to the public generally, and the public is thus entitled to initiate agency review of such decisions.

See 42 Fed. Reg. 4684 (Jan. 25, 1977)

19. Additionally, agency policy specific to 21 CFR 601.25 dictated that FDA offer an opportunity for public comment since the Final Rule's conclusions with respect to efficacy and its omission of a "risk-benefit ratio" differed from the Proposed Rule: "The opportunity to comment is particularly important where the agency disagrees with the recommendation of a panel." See 47 Fed. Reg. 44062, et. seq.(para 18)(Oct. 5, 1982).

20. In contrast, FDA's failure to offer a new comment period prior to promulgating its 2004 AVA Final Rule, and its assertion that the comment period afforded after the 1985 Proposed Rule suffices, is inconsistent with agency past practice. These practices are intended to provide citizens every opportunity for "due process" because "final agency action" on drug and vaccine licenses carries the weight of law, and once established is difficult to overturn.

b. FDA's Administrative Record in support of its Final Rule is wholly inadequate.

21. In FDA's previously cited 1977 explanation of administrative practices, the Commissioner specifically sought to "encourage persons to participate at the administrative level and to advance all information and arguments at that point" to as to "guarantee to a court a fixed and complete record on which to base its review." See 42 Fed. Reg. 4688. Further, in requiring those who submit citizen petitions to provide a balanced review of all information pertinent to an administrative rulemaking, FDA established a standard the agency has failed to meet in its Administrative Record on AVA:

> Equally important is the failure of the comments to recognize that divulging adverse information may advance rather than detract from a participant's position. The administrative record of a particular matter may contain information adverse to the Commissioner's decision and still be legally sufficient to support the decision...What the comments overlook is that a decision favorable to a petition that reflects a review of information and arguments both supportive of and adverse to the petition is likely to be more credible, and ultimately more supportable, than a decision reached on the basis only of supportive information.

Id. at 4686.

22. There are many possible sources of additional information that might have come to light had FDA provided a comment period and sought "arguments both supportive of and

adverse" to its Final Rule.[12] The one obvious example would be the other Brachman, et.al. articles not cited in either the 1985 Proposed Rule or the 2004 Final Rule. Defendants' arguments seem to imply that the "Brachman study" equates solely to the April 1962 article cited in the Proposed and Final Rules. In fact, the "study" was the late 1950's field trial, and all of the articles Brachman, et.al. published should have been considered by FDA in its Administrative Record. Of particular note is Brachman's December 1960 article[13], which offers a much different view on efficacy than that suggested in FDA's Final Rule. In this article, Brachman stated:

> However, if only the job categories which are associated with a high risk of developing anthrax are studied, *then no conclusion with respect to the effectiveness of the vaccine can be drawn*, as shown in table 4.

Brachman, et.al., Dec. 1960 at 14(emphasis added)

> *The efficacy of the anthrax cell-free antigen as a vaccine was not fairly tested in this epidemic*. Although none of the 9 cases occurred in vaccinated individuals, only approximately one fourth of the employees had received the vaccine. There was an apparent difference in attack rates between workers who received placebo inoculations and those who received vaccine, but *analysis of their job categories suggested that the vaccinated group was not at as high a risk as the placebo or uninoculated control groups*.

Id. at 20 (emphasis added).

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[12] Defendants' apparent outright rejection of Dr. Schumm's manuscript (See Def. SJ Reply at 3-4, Apr. 21, 2004) also runs counter to the same 1977 FDA statement on administrative practices mentioned above: "The Commissioner also rejects the suggestion that only scientifically backed adverse information should be required to be included. Issues that come before the Commissioner rarely turn on definitive or uncontradicted evidence, and *adverse educated opinion*, even if lay opinion, *should be included* if for no other reason than to permit the agency to explore the matter further if it so desires. See 42 Fed. Reg. at 4686.

[13] Brachman, et.al., "An Epidemic of Inhalation Anthrax. II. Epidemiology", Am. Jnl. of Hygiene (Dec 1960), Vol. 72, p. 6-23.

> *Anthrax vaccine* containing alum-precipitated protective antigen *appeared to afford protection to those who received it, but this impression could not be confirmed statistically*. Previous inapparent infection...also may have protected some of the workers.

Id. at 21 (emphasis added).

23. FDA's failure to both include this article in the Administrative Record or to explain why FDA's conclusions in the Final Rule were so at odds with Brachman's published findings cannot be viewed by the Court as a simple oversight. While there may be subjective debate on other sources that might have been included in the Administrative Record, Brachman's December 1960 article goes to the foundation of the Defendants' arguments. Absent convincing information to the contrary, the Brachman, et.al. December 1960 article undermines Defendants' assertions that:

- "FDA's effectiveness determination is fully, and adequately, supported by the Brachman study, upon which FDA relied for proof of AVA's effectiveness under Section 601.25(d)(2)." See Def. Opp. S.J. at 18 (Apr. 7, 2004).
- "Although the IOM report and animal studies corroborated FDA's effectiveness decision, see id., the Order plainly can be "supported without [them]." Id.

c. FDA's 2004 Final Rule on AVA violates a statutory mandate to provide a risk-benefit analysis.

24. Defendants in this case have made several statements asserting that safety is not at issue, just efficacy. While I am not qualified to comment on AVA's safety, I would simply state that safety cannot not be at issue. This was made clear in the 1972 FDA policy that led to the regulation (21 CFR 601.25) under which FDA's review of AVA was to have been conducted:

> Although these products have been reviewed for safety in the past, it is concluded that the safety of these products should be reviewed again at this time, not only because *a review of effectiveness requires a consideration of safety factors*, but also because new safety criteria have been developed

> relating to the necessity for long term scientific evaluation, in that *long periods of time may pass before latent adverse effects become manifest*.

See 37 Fed. Reg. 16679 (Aug. 18, 1972)(emphasis added).

25. Recognizing the importance of safety, the 1985 Proposed Rule complied with the 1962 Harris-Kefauver Act mandate that FDA provide an analysis of relative safety, expressed as a "risk-to-benefit ratio", stating:

> …safety of this product is not a major concern, *especially considering its very limited distribution*…This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. *The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use*.

See 50 Fed. Reg. 51058-51059 (Dec. 13, 1985).

26. In fact, even in 1985 the only practical market for the vaccine was the military because, as the Proposed Rule noted, "the industrial setting in which the [Brachman and CDC] studies were conducted is vanishing." See Id. at 51058. See also AR 338.

27. The Final Rule also seemingly ignored the 2002 FDA-approved AVA package insert, which contains restrictive language similar to the 1985 Proposed Rule:

> BioThrax [AVA] is also *indicated for individuals at high risk of exposure* to Bacillus anthracis spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials. Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

See Biothrax package insert (Jan 2002)[emphasis added].[14]

28. FDA's continued acquiescence in allowing DoD to unilaterally define "high risk," in the apparent absence of an anthrax threat, is an abrogation of its regulatory responsibility. GAO issued three reports from 1999-2002 that make clear that the military threat from anthrax has not changed since the end of the Cold War, during which anthrax

[14] See *http://www.fda.gov/cber/label/biopava01310022LB.pdf*.

vaccine was not used in a mandatory vaccination program like AVIP. The most recent GAO report states:

> As of October 2002, intelligence assessments have not changed since 1990 for chemical and biological warfare threats on the battlefield or by terrorists, [sic] This is especially true, intelligence analysts told us, in terms of the numbers of countries suspected of developing anthrax spores, the types of biological agents these countries are known to possess, and their ability to weaponized and deliver such agents. Unfortunately, for assessing a similar nonbattlefield threat, there are no current data on which to base an estimate apart from data from the October 2001 attack.

See "Diffuse Security Threats: Information on Domestic U.S. Anthrax Attacks", GAO-0-323T (Dec. 10, 2002), at Attachment "D".[15]

29. The Court should note that DoD is moving away from this threat – based use of investigational medications. On May 20, 2003 the Armed Forces Epidemiology Board[16] was briefed on a May 13, 2003 memorandum by Deputy Secretary Wolfowitz suggesting DoD modify its immunization policy (DoD Directive 6200.2) from a so-called "threat-based" policy to a "capabilities-based" policy. This means that DoD intends to vaccinate simply because it has vaccine available, regardless of a threat, a policy that ignores the potential risk in any vaccine.[17]

30. If the Final Rule had kept the same risk-benefit ratio as the 1985 Proposed Rule, a mandatory DoD anthrax vaccine immunization policy in the absence of a threat would be

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[15] See also GAO-T-NSIAD-99-148, "Medical Readiness: Safety and Efficacy of the Anthrax Vaccine," at 2, Apr. 29, 1999, at *http://www.gao.gov/archive/1999/ns99148t.pdf;* GAO-02-445, "Anthrax Vaccine: GAO's Survey of Guard and Reserve Pilots and Aircrew", at 3 (Oct. 23, 2002), at *http://www/gao.gov.new.items/d02445.pdf.*

[16] See *http://www.ha.osd/mil.afeb/.*

[17] See LtCol Donald L. Noah, USAF, slide briefing to the Armed Forces Epidemiology Board, May 20, 2003, at *http://www.ha.osd.mil/afeb/meeting/052003meeting/AFEB%20 May%202003%20 Day%201%20LtCol%20Noah.ppt.*

an experimental use and a clear violation of federal law. So, it appears FDA omitted a statement on risk-benefit from the Final Rule to allow DoD to vaccinate in legal ambiguity – until, or unless, someone challenged the Final Rule.

31. Additionally, FDA failed to consider recent Vaccine Adverse Event Reporting System (VAERS) reports in its Administrative Record. This is highly significant, since the 2002 IOM Report upon which FDA relies so heavily assumed that post-renovation vaccine would be safer, but cautioned "individuals receiving these lots should be monitored for possible acute or chronic adverse events of immediate or later onset." See IOM Report at 16.[18] Contrary to this advice, it appears that in FY2005 DoD may not fund Congressionally-mandated[19] "Vaccine Healthcare Centers" at Walter Reed Army Medical Center and elsewhere.[20] These centers have developed a unique expertise at documenting the types of adverse events the IOM Report said should be monitored.

d. FDA's extended delay in ruling on AVA's license creates a potential for court review.

32. In 1977, the Commissioner acknowledged "delay of action by FDA so substantial as to constitute denial of relief requested" was "potentially subject to judicial review." See 42 Fed. Reg. 4688 (Jan 25, 1977) Significantly, FDA's actions show an improper delay in performance of its regulatory responsibilities with respect to AVA.

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[18] See *http://books.nap.edu/books/0309083095/html1/16.html#pagetop.*

[19] Public Law 106-398, Section 751, Oct. 30, 2000.

[20] David Ruppe, "U.S. Army Provides No Funds for Vaccine Care Centers", *Global Security Newswire,* May 18, 2004, at *http://www.nti.org/d_ newswire/issues/2004/5/18/ b047b91a-baae-4469-a369-ce894037d5a1.html.*

33. For instance, the mid-2003 exchange of letters[21] between Assistant Secretary of Defense Dr. Winkenwerder and former Commissioner McClellan was virtually identical to the 1997 Joseph-Friedman exchange. See AR 4031-4032. Like his predecessor, Commissioner McClellan once again refused to implement "final agency action," either by issuing an "advisory opinion" (21 CFR 10.85) or by completing a Final Rule (21 CFR 601.25), apparently because any such "final agency action" would be subject to challenge. Given the on-going litigation in Doe v. Rumsfeld, this can only be seen as an attempt to sustain the legally ambiguous situation that had existed for 18 years since the 1985 Proposed Rule.

34. More disturbing is the FDA paperwork exercise that ensued after the Court's December 22, 2003 injunctive relief. The markings on the original version[22] of the FDA Final Rule indicate that the Associate Commissioner for Policy, Mr. Shuren, signed it (at p. 41) on December 23, 2003 -- less than 24 hours after the Court's ruling. (This quick response contrasts with the two months it took Commissioner McClellan to answer Dr. Winkenwerder's letter in the exchange mentioned above). While it is possible FDA was coincidentally about to issue a Final Rule on AVA, it seems likely that the agency simply had a draft ready to use only in the event the Court forced its hand. The pen-and-ink addition of "and Final Order" was not added to FDA's ruling until six days later by an FDA employee (see margins, "B. Suhre", "OFR", "12-29"). Thus, FDA's action was, in keeping

[21] See Attachment to Winkenwerder declaration (Dec. 30, 2003).

[22] "ACTION: Final rule" (with "and Final Order" added as a pen and ink change on Dec. 30, 2004)(Note: while still on the FDA website, this version is not in the online docket.). See *http://fda.gov/OHRMS/DOCKETS/98fr/80n-0208-nfr0001.pdr*.

with agency policy, intended to be a “Final Rule” simply because it was an exercise in administrative rulemaking.

I do hereby affirm under the penalties of perjury and upon personal knowledge that the contents of the foregoing are true and correct to the best of my knowledge and belief.

Date: June 7, 2004.

/s/

Sammie R. Young (Colonel, USAFR, (MSC) ret.)
former Director, Division of Compliance, FDA Bureau of Biologics
former Deputy Director, Office of Compliance, FDA Center for Drug Evaluation and Research (CDER)

REPORT TO THE SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND GOVERNMENT RESEARCH COMMITTEE ON GOVERNMENT OPERATIONS UNITED STATES SENATE

Problems Involving The Effectiveness Of Vaccines

B-164031(2)

National Institutes of Health
Department of Health, Education, and Welfare

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

MARCH 28, 1972

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

Dear Mr. Chairman:

Pursuant to your request of June 28, 1971, this is the second in a series of reports relating to activities of the Food and Drug Administration and the Division of Biologics Standards, National Institutes of Health. Our first report, entitled "Answers to Questions on the Investigational Use of Isoniazid--a Tuberculosis Control Drug," was issued to you on October 7, 1971. A third report will be issued to you on the regulation by the Division of Biologics Standards of adenovirus, adenovirus-influenza, and pertussis vaccines.

This report is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and general use of influenza virus vaccines. As agreed upon with your office, we discussed our report with officials of the National Institutes of Health but did not obtain their formal written comments.

We plan to make no further distribution of this report unless copies are specifically requested, and then we shall make distribution only after your agreement has been obtained or public announcement has been made by you concerning the contents of the report.

Sincerely yours,

Elmer B. Staats

Comptroller General
of the United States

C1+R The Honorable Abraham A. Ribicoff
Chairman, Subcommittee on Executive
Reorganization and Government Research
Committee on Government Operations
United States Senate

501511

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ABBREVIATIONS

CCA Chicken cell agglutination

DBS Division of Biologics Standards

FDA Food and Drug Administration

GAO General Accounting Office

HEW Department of Health, Education, and Welfare

NIH National Institutes of Health

COMPTROLLER GENERAL'S
REPORT TO THE SUBCOMMITTEE ON
EXECUTIVE REORGANIZATION
AND GOVERNMENT RESEARCH
COMMITTEE ON GOVERNMENT OPERATIONS
UNITED STATES SENATE

PROBLEMS INVOLVING
THE EFFECTIVENESS OF VACCINES
1 National Institutes of Health 28
2 Department of Health, Education, 22
and Welfare B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

The Chairman of the Subcommittee on Executive Reorganization and Government Research, Senate Committee on Government Operations, asked the General Accounting Office (GAO) to review selected aspects of Federal control over drugs and biological products (vaccines, serums, etc.). This report, the second report to be issued to the Chairman, is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and use of influenza vaccines.

Background

Pursuant to the Public Health Service Act, biological products must be licensed by the Secretary of the Department of Health, Education, and Welfare (HEW) before they may be transported interstate. To obtain licenses manufacturers must produce products which meet standards of safety, purity, and potency (the ability of products to produce given results). The Division of Biologics Standards (DBS), a division of the National Institutes of Health (NIH), licenses biological products.

FINDINGS AND CONCLUSIONS

Need to remove ineffective products from interstate commerce

Although the Office of the General Counsel of HEW concluded on several occasions that legislative authority existed under the Federal Food, Drug, and Cosmetic Act that could prevent ineffective biological products from being introduced into interstate commerce, DBS disagreed with the Office of the General Counsel. (See p. 11.)

The disagreement apparently was resolved by the Secretary in November 1971. The Secretary stated at that time that DBS, in practice, had been exercising the efficacy authority under the Federal Food, Drug, and Cosmetic Act. Although GAO found no evidence of any ineffective products licensed after 1962, GAO did find that ineffective products licensed prior to 1962 were being marketed. (See p. 13.)

MARCH 28, 1972

On February 25, 1972, the Secretary took action to require NIH, through an appropriate delegation of authority, to apply the provisions of the Federal Food, Drug, and Cosmetic Act to biological products.

Release of subpotent influenza vaccines

DBS was releasing lots of influenza vaccines even when its tests showed the potency of the vaccines to be as low as 1 percent of the established standards. Of 221 lots released during 1966, 1967, and 1968, 130 failed to meet the standards. (See p. 17.)

Subpotent vaccines were released because agency employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to the standards. DBS says that its tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. (See p. 17.)

Effectiveness and use of influenza vaccine

Scientific studies disagree significantly as to the specific degree of effectiveness of the vaccines. In addition, in periods of epidemic, there may be a problem with the vaccines' unavailability to persons in high-risk groups for whom the vaccines are needed, because persons receive the vaccines who do not need them. (See p. 22.)

Several Federal agencies notified their employees of the availability of the vaccines but did not make known the recommendations of the Public Health Service Advisory Committee on Immunization Practices regarding the types of persons that should be inoculated. This committee was established by the Surgeon General to develop recommendations for the use of the principal biological products. (See p. 24.)

RECOMMENDATIONS OR SUGGESTIONS

HEW should:

--Require NIH to establish milestones to implement the efficacy provisions of the Federal Food, Drug, and Cosmetic Act.

--Monitor NIH's progress in stopping the marketing of biological products determined to be ineffective.

--Require DBS to revise its instructions to provide sufficient controls to preclude vaccines from being released if tests by either the manufacturers or DBS show the vaccines to be subpotent.

--Fully inform Federal employees of the limitations and merits of receiving influenza virus vaccines and of the annual recommendations of the Public Health Service Advisory Committee on Immunization Practices.

MATTERS FOR CONSIDERATION BY THE SUBCOMMITTEE

The Subcommittee should consider bringing GAO's recommendations to the attention of the Secretary of HEW so that the recommendations may be implemented.

CHAPTER 1

INTRODUCTION

On June 28, 1971, the Chairman of the Subcommittee on Executive Reorganization and Government Research, Committee on Government Operations, United States Senate, requested that we review selected activities of the Food and Drug Administration (FDA) and of the Division of Biologics Standards of the National Institutes of Health, Department of Health, Education, and Welfare. (See app. I.) To comply with the Chairman's request, we agreed to issue three separate reports. The first was issued on October 7, 1971, entitled "Answers to Questions on the Investigational Use of Isoniazid--a Tuberculosis Control Drug."

This report is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and general use of influenza virus vaccines. We plan to issue a third report on DBS's regulation of adenovirus, adenovirus-influenza, and pertussis vaccines.

HEW'S RESPONSIBILITIES FOR THE REGULATION OF BIOLOGICAL PRODUCTS AND DRUGS

The Secretary of HEW is responsible for the regulation of biological products and drugs through two statutes--section 351 of the Public Health Service Act, as amended (42 U.S.C. 262), and the Federal Food, Drug, and Cosmetic Act of 1938, as amended (21 U.S.C. 301).

Biologics

Section 351 of the Public Health Service Act provides that all biological products[1] and their manufacturers be

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[1]A "biological product" is defined under the Public Health Service Act as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analagous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man."

licensed by the Secretary of HEW before the products can be sold in the District of Columbia or transported interstate. Before the products can be licensed, they must meet standards designed to ensure their continued safety, purity, and potency. The Secretary is authorized to inspect the licensed establishments, as well as any establishments being considered for licensing, to ensure that they conform to the legislation and regulations applicable to the manufacture of biological products. As of May 1971, 263 biological products were licensed and 235 establishments were licensed to manufacture such products.

The responsibility for administering section 351 has been delegated by the Secretary to the Director of NIH. DBS, a division of NIH, is the organizational entity which carries out this responsibility. DBS was appropriated $8.8 million for fiscal year 1971.

The Code of Federal Regulations (42 CFR 73) states that a licensed product may not be released by a manufacturer for sale until the manufacturer has completed tests to determine that the product conforms to the standards applicable to its safety, purity, and potency.

"Safety" is defined in the regulations as the relative freedom from harmful effects to recipients. Closely allied to safety is the requirement for "purity"--the relative freedom from extraneous matter in the finished product. "Potency" is defined as the ability of the product to effect a given result, as indicated by laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended.

DBS may require a manufacturer to submit, prior to the release of a product to the public, samples of production lots and the related protocols which present the results of the manufacturer's tests. When protocols are required, DBS reviews them and may conduct a series of tests within its own laboratories to verify the results shown. DBS then may either release a lot or reject it when necessary to ensure the safety, purity, or potency of the product.

In 1964 the Surgeon General established the Public Health Service Advisory Committee on Immunization Practices--

composed of persons from the fields of public health, medicine, and research--to develop recommendations for the use of the principal biological products in the United States.

Drugs

The Secretary of HEW has delegated his responsibility for administering the Federal Food, Drug, and Cosmetic Act of 1938 to FDA.

Under the provisions of this act, a "drug" is defined as:

> "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories."

Section 505(a) of the act requires, among other things, that a manufacturer of new drugs or any other person seeking to distribute drugs file an application--showing that the drug is safe and effective--with FDA and obtain its approval before the products may be introduced into interstate commerce. Section 505(b) requires that FDA approve the drug for both safety and efficacy.

Influenza

Influenza is an infectious disease, lasting from a few days to 2 weeks, which affects the respiratory systems of persons. There are two primary types of influenza--types A and B--each of which has a number of strains. Strains are the different influenza organisms which have been isolated and identified as causing influenza infection. Influenza

virus vaccines are biological products designed to combat the particular strain or strains causing the disease.

The first license for the manufacture and use of influenza virus vaccine was issued in 1945. As of December 1971, eight establishments were licensed to manufacture the vaccines and six actually were engaged in producing and marketing the vaccines. From 1966 through 1970 about 112 million doses of the vaccines were distributed in the United States.

Potency standards for influenza virus vaccines

DBS issues annual potency standards to the manufacturers of influenza virus vaccines. For 1966 the standards required that a manufacturer's product be at least equal to the strength of a DBS reference vaccine, except for one strain which had to be five times the strength of the reference vaccine. The reference vaccine is a standardized vaccine sent to the manufacturers by DBS to be used as a basis for comparision with manufacturers' products.

In 1967 a manufacturer's vaccine was required to be at least equal to the potency of the reference vaccine. Standards for 1968 required that the potency of all strain components of the vaccine, except one, be equal to or greater than the potency of the reference vaccine. The one exception was for a strain to combat a 1968 epidemic; DBS required that the potency of this strain be at least 75 percent of the reference vaccine.

The standards established by DBS for 1969, 1970, and 1971 required that a manufacturer's product be at least 75, 80, and 85 percent as potent, respectively, as the reference vaccine to be satisfactory for release.

DBS requires that protocols and a sample of a manufacturer's vaccine be submitted to it for review and approval before the vaccine is released to the public.

Tests to determine potency

To determine whether the individual lots of manufacturers' vaccines meet the established potency standards, DBS requires the manufacturers to perform certain laboratory tests on the lots. DBS performs similar tests in its laboratories for selected lots.

During 1966, 1967, and 1968, DBS required the manufacturers to determine the potency of their vaccines by means of mouse potency tests, which involved inoculating one group of mice with the manufacturers' vaccines and another group with the DBS reference vaccine. After inoculation, each group of mice was injected with the influenza virus and the protective ability afforded by each vaccine was compared.

Late in 1968 DBS changed the required test to the chicken cell agglutination (CCA) test, which determined virus concentration by measuring the ability of the virus to clump red blood cells. This ability is proportional to the number of virus particles. The test is performed on both the manufacturers' vaccines and the DBS reference vaccine, and the results are compared to determine whether the manufacturers' vaccines achieve the potency standard established by DBS.

Instructions relating to release of influenza virus vaccines

DBS instructions relating to the release of vaccines are contained in a Viral and Rickettsial Control Test Check List, dated November 1965, which stipulates that final release action is to be based on the recommendations of the responsible DBS test operators in each laboratory performing vaccine testing. The information required for release is (1) the approval of the manufacturer's test results for compliance with the regulations and requirements and (2) the results of DBS confirming tests, if performed.

Other vaccine release instructions are contained in a 1962 DBS memorandum on influenza potency testing. This memorandum states that the release of influenza virus vaccines is to be based on the data submitted by the

manufacturers and is not to be based on any tests performed by DBS. The memorandum states also that DBS potency tests are not intended to provide data for either release or rejection of a lot but are to have as their objective "the establishment of demonstrated reproducibility of technical procedures employed by the manufacturer and DBS."

In 1971 DBS clarified the contents of the 1962 memorandum by stating that it released lots on the basis of satisfactory information furnished by the manufacturers and that tests performed by DBS were a mechanism for being sure that the manufacturers could perform tests and that the results of the tests could be relied upon.

CHAPTER 2

NEED FOR ACTION TO REMOVE INEFFECTIVE BIOLOGICAL PRODUCTS FROM INTERSTATE COMMERCE

We believe that there is a need for DBS to (1) require that biological products be effective prior to licensing and (2) take action to remove from interstate commerce those licensed products that are not effective.

We found that 75, or about 28 percent, of the 263 biological products licensed by DBS generally were not recognized--according to the Director of DBS--as being effective by most of the medical profession. All 75 of the products were licensed by DBS prior to the 1962 amendment to the Federal Food, Drug, and Cosmetic Act discussed on page 12.

DBS has not required biological products to be effective as a condition of licensing and has not removed ineffective products from interstate commerce, because it did not believe that legislative authority existed for such actions.

HEW's Office of the General Counsel has expressed its opinion to DBS on several occasions that the Federal Food, Drug, and Cosmetic Act provides authority to require that licensed biologics be effective. DBS, however, has disagreed with the opinion of the Office of the General Counsel and believes that legislation is needed to require biological products to be effective.

As a result of the interest in the efficacy of biological products expressed by the Chairman of the Subcommittee on Executive Reorganization and Government Research of the Senate Committee on Government Operations, the Secretary of HEW advised the Chairman, on November 29, 1971, that legislation requiring biologics to be effective was not needed because sufficient authority existed under the Federal Food, Drug, and Cosmetic Act and that, in practice, DBS had been exercising such authority.

Although the Secretary apparently has resolved the disagreement between the Office of the General Counsel and DBS

regarding the authority to require biologics to be effective, it is our opinion that DBS has not been fully exercising this authority.

APPLICABILITY OF EFFICACY PROVISIONS OF FEDERAL FOOD, DRUG, AND COSMETIC ACT TO BIOLOGICAL PRODUCTS

The Federal Food, Drug, and Cosmetic Act requires that the Secretary approve a drug for safety and efficacy before it may be introduced into interstate commerce. The requirement for efficacy was added to the act by an amendment dated October 10, 1962 (76 Stat. 781), and was to be applied to (1) all drugs approved subsequent to October 10, 1962, and (2) any drugs approved during the period June 25, 1938, to October 10, 1962, which generally were not recognized by scientific experts to be effective in use.

According to the Office of the General Counsel, drugs, as defined in the act, include biological products and the authority to require biological products to be effective as a condition of licensing can be delegated to NIH by the Secretary.

DBS did not agree with the opinion of the Office of the General Counsel that a delegation of authority from the Secretary would be satisfactory and, from 1964, recommended to the Department that legislation be proposed to the Congress that would require biologics to be effective in use.

On February 28, 1969, for example, the Office of the General Counsel advised the Director of DBS that the Secretary could delegate to NIH the authority to administer, apply, and enforce the efficacy provision of the Federal Food, Drug, and Cosmetic Act with respect to all drugs which are biological products. This authority included (1) refusing to approve an application for the introduction of a drug into interstate commerce if the drug was not effective for use and (2) withdrawing a previous drug approval if the drug was discovered to be not effective in use.

On July 30, 1969, the Director of DBS advised the Director of the Office of Legislative Analysis, NIH, that he

disagreed with the opinion of the Office of the General Counsel. He said that, although it might be possible to require that future biological products be effective, he did not believe that it was possible to require products already licensed to meet current concepts of efficacy. Regarding the delegation of the authority of the Federal Food, Drug, and Cosmetic Act, the Director of DBS stated that:

> "In view of the continuing undercurrent recommending the combining of the DBS with Food and Drug, we are quite reluctant to request such a delegation since it would offer an excellent opportunity of such proponents to renew their effort in creating one control agency."

Because the Chairman of the Subcommittee on Executive Reorganization and Government Research, Senate Committee on Government Operations, expressed interest in HEW's authority to require biological products to be effective in use, the Secretary requested the views of the Office of the General Counsel.

In a memorandum dated November 23, 1971, the General Counsel concluded that from 1962 HEW had the authority to require that biological products be effective in use but that the authority had not been delegated to DBS. The General Counsel stated that from 1962 DBS did not license any products which were not effective and that DBS therefore acted substantially as though it did have the authority to require that biological products be effective. The General Counsel recommended that the Department delegate to DBS the authority to continue this informal practice.

The General Counsel also advised the Secretary that he was working out the details for the delegation of authority to the Director of NIH. On February 25, 1972, the delegation of authority was effected.

On November 29, 1971, the Secretary forwarded the General Counsel's opinion to the Chairman and stated that sufficient regulatory authority existed under the Federal Food, Drug, and Cosmetic Act to require biologics to be effective and that, in practice, DBS had been exercising such authority.

PRODUCTS NOT GENERALLY RECOGNIZED AS BEING EFFECTIVE

In a memorandum dated November 19, 1969, to the Office of Legislative Analysis, NIH, the Director of DBS stated that there were several biological products which had been licensed for many years but which had been considered as not effective in use by most of the medical profession.

DBS officials provided us with a list of the products referred to by the Director of DBS. The list showed that there were 75 licensed biological products--about 28 percent of the 263 licensed biological products--which generally were recognized as not being effective in use. Because some of the licensed products are produced by more than one manufacturer, a total of 132 licenses--42 of which were issued between June 1938 and October 1962--have been issued for production of the 75 products. According to DBS these licenses are for biological organisms which may be sold to the public individually or combined with other organisms.

DBS provided us also with a list of vaccines being sold to the public that contain one or more of the 75 licensed organisms generally recognized to be not effective in use. The list (see app. II) showed that, as of December 31, 1971, there were 32 such vaccines. Of these 32 vaccines, 16 contained organisms which were licensed after 1938. We noted, however, that one of the 32 vaccines contained a biological organism which was not on the list of 75 organisms supplied to us by DBS.

We noted also that the package circulars for the ineffective vaccines indicated that persons might suffer adverse reactions from the use of the vaccines. For example, one of the vaccines--sold for the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections--is made up of six ineffective organisms which were licensed by DBS in 1956. The package circular, which accompanies the sale of this vaccine, states that, although significant side effects from the vaccine are uncommon, there have been reports of children who have developed systemic reactions--consisting of fever, rash, abdominal cramps, and diarrhea--4 to 8 hours after injection.

The package circular for another of the ineffective vaccines--intended for the treatment of infections and inflammations of the eye by creating a fever in the patient--states that:

> "The febrile reaction following intravenously administered *** [vaccine] usually occurs in four to eight hours and in most cases is not preceded by a chill. The temperature may rise to 101° F. or even 104° F. Fever subsides in a few hours, and the patient is left with muscular pains. Chilly sensations and malaise may be expected. *** The patient should be kept under close observation through the period of increased temperature, and if excessive fever occurs, it should be combated vigorously."

CONCLUSIONS

Although the Office of the General Counsel concluded on several occasions that legislative authority existed that could prevent ineffective biological products from being introduced into interstate commerce, DBS disagreed with the conclusion of the Office of the General Counsel.

The disagreement apparently was resolved by the Secretary in November 1971. The Secretary stated at that time that DBS, in practice, had been exercising the efficacy authority contained in the Federal Food, Drug, and Cosmetic Act. Although we found no evidence of any ineffective products licensed after 1962, ineffective biological products licensed prior to 1962 are being marketed.

We noted that the Secretary took action to require NIH, through an appropriate delegation of authority, to apply the provisions of the Federal Food, Drug, and Cosmetic Act to biological products. We believe, however, that, having made this determination, the Secretary also should (1) require NIH to establish milestones to implement this authority and (2) monitor NIH's progress in stopping the marketing of ineffective biological products.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that, to stop the marketing of ineffective biological products, HEW (1) require NIH to establish milestones to implement the efficacy provisions of the Federal Food, Drug, and Cosmetic Act and (2) monitor NIH's progress in stopping the marketing of biological products determined to be ineffective.

CHAPTER 3

RELEASE OF SUBPOTENT INFLUENZA VIRUS VACCINES

Manufacturers' test results showed that 115 of 221 lots of influenza virus vaccines released by DBS during 1966, 1967, and 1968 failed to meet potency standards established by DBS. In addition, 15 other lots which were released and shown to be potent by the manufacturers' tests were found to be subpotent on the basis of DBS tests. We found no indications that subpotent vaccines were released in 1969 or 1970. Only one subpotent lot, however, was submitted by manufacturers during this period.

It appears that subpotent vaccines were released because DBS employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to potency standards established by DBS.

DBS instructions state that its tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. We believe that the instructions should be revised to provide that vaccines not be released if tests by either the manufacturers or DBS show the vaccines to be subpotent.

NEED TO REVISE INSTRUCTIONS

DBS instructions state that final release actions for lots of influenza virus vaccines are to be based on the recommendations of responsible operators in the DBS laboratories which review the manufacturers' test results. The instructions state also, among other things, that the laboratory operators must record any lot which fails to meet the potency standards.

We found, however, that, for lots released on the basis of manufacturers' tests, DBS laboratory operators indicated the failure to meet DBS potency standards for only 25 of the 115 subpotent lots during 1966, 1967, and 1968. In addition, DBS records contained information explaining the

release of 35 subpotent lots, which, in our opinion, was questionable; we found no documentation explaining the release of the other lots.

For example, 11 lots were released on the basis of the manufacturers' certifications to the Director of DBS that the vaccines had been manufactured in compliance with the formula issued by DBS. Also another lot was released by the Assistant Director of DBS even though the DBS laboratory operator had noted that the potency of a particular strain was unsatisfactory. The DBS laboratory operator had recommended that this lot be rejected because, according to the manufacturer's tests, one of the component strains was only 45 percent as potent as the reference vaccine.

The Assistant Director released this lot because, in his opinion, it met the minimum potency requirements set forth in section 4.25 of the instructions sent to the manufacturers by DBS. Section 4.25 states that the tests performed by manufacturers must be based on comparisons of their vaccines with the reference vaccine of DBS and that the results of the potency tests must show that the manufacturers' vaccines are at least equal to the reference vaccine.

We found that the DBS laboratory operators recorded as satisfactory 82 of the 115 lots that had potency values which were less than the DBS standards.

For example, one lot released by DBS on January 18, 1966, was designed to combat six strains of influenza. The manufacturer's test showed that one of the six strains was only 19 percent as potent as the reference vaccine and that the other five strains were at least equal to the reference vaccine.

DBS tested the potency of five of the six strains and found the potency of the strain noted as 19 percent on the manufacturer's tests to be greater than 300 percent of the reference. These same DBS tests indicated, however, that three of the four remaining strains had potency values below 20 percent of the reference vaccine and that the fourth strain had a potency value of approximately 50 percent of the reference vaccine. The laboratory operator recorded

that the potency of this lot was satisfactory on the basis of the DBS test, and the lot was released.

In connection with the release of subpotent lots, we have noted that DBS instructions state that DBS tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon.

Variability of test results

DBS tested 78 of 221 lots of vaccines released during 1966, 1967, and 1968. We found that 41 of these lots met the DBS potency standards and that 34 of the 41 were shown to be potent by the manufacturers' tests. The remaining 37 lots tested by DBS did not meet its potency standards. According to the manufacturers' test results, 22 of these lots were subpotent and 15 were potent. We found also that DBS test results varied significantly from the test results of the manufacturers.

For example, a manufacturer's tests for a lot released by DBS on September 13, 1967, showed potent strain values of 100 percent, 171 percent, and 149 percent whereas the DBS tests on the same lot showed subpotent values of 0.8 percent, 15 percent, and 12 percent, respectively.

This lot was released with a notation that potency was satisfactory on the basis of the manufacturer's tests even though (1) the potency standard at that time required these strains to be at least equal to the reference vaccine and (2) the DBS test results differed significantly from those of the manufacturer.

Reliability of mouse potency test

The laboratory chief responsible for potency testing since 1967 advised us that, due to problems with the variability of the results of the mouse potency tests, DBS did not strictly apply its potency standards during 1967 and 1968.

The laboratory chief advised us also that the mouse potency test was considered unreliable, and he furnished us with a 1969 report prepared by officials of DBS that questioned the reliability of the mouse potency test. The report concluded that the CCA test, which was adopted by DBS late in 1968, was a more reliable means for measuring potency. The laboratory chief advised us, however, that he also used the CCA test--at times subsequent to release--to determine the potency of selected influenza vaccine lots, including 55 subpotent lots submitted by the manufacturers during 1966, 1967, and 1968. The results of the CCA tests showed that 48 of the 55 lots still failed to meet the potency standards established by DBS.

The laboratory chief furnished us also with a memorandum dated July 12, 1968, in which he advised the Director of DBS that, with the exception of one manufacturer, the first lots submitted during 1968 showed that nothing was being done to increase the potency of the vaccines. The laboratory chief said in the memorandum that "it would be sad if we allow the manufacturers to make and sell poor influenza vaccines for another season."

CONCLUSIONS

We believe that, because of the significance of the ability of biological products--including vaccines--to effect a given result, it is important that DBS develop standards for the products that are designed to protect the consumer and strictly enforce such standards. We found, however, that DBS was releasing lots of influenza virus vaccines during 1966, 1967, and 1968, even when its tests showed the potency of the vaccines to be as low as 1 percent of the established standards. There were no indications that subpotent vaccines were released in 1969 or 1970. Only one subpotent lot, however, was submitted during this period.

It appears that subpotent vaccines were released because DBS employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to potency standards established by DBS.

A DBS instruction states that DBS potency tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. We believe that this instruction should be revised to provide that a vaccine not be released if tests by either the manufacturer or DBS show the vaccine to be subpotent.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that HEW require DBS to revise its instructions to provide sufficient controls to preclude vaccines from being released if tests by either the manufacturers or DBS show the vaccines to be subpotent.

CHAPTER 4

PROBLEMS IDENTIFIED WITH EFFICACY AND GENERAL USE OF INFLUENZA VIRUS VACCINES

We found that the conclusions of scientific studies disagreed significantly as to the specific degree of effectiveness of the influenza virus vaccines. We found also that a number of Federal agencies--in connection with in-house influenza inoculation programs--had notified their employees of the availability of the vaccines but had not made known the recommendations of the Public Health Service Advisory Committee on Immunization Practices regarding the types of persons that should be inoculated.

EFFICACY OF INFLUENZA VIRUS VACCINES

Information on the effectiveness of influenza virus vaccines is conflicting. DBS officials estimated that influenza virus vaccines were 50 to 60 percent effective, and they provided us with several studies concerning the efficacy of the vaccines. One of the studies, performed by researchers at Mount Sinai School of Medicine, City University of New York, and at the California State Department of Public Health showed that, at one military base, influenza vaccines were 73 percent effective in reducing the number of trainees hospitalized in 1970.

Other reports, however, indicated a lesser degree of effectiveness. For example, a report published in 1964 by officials of the HEW National Communicable Disease Center[1]--which is responsible for coordinating and evaluating a national program for the prevention and control of communicable diseases, such as influenza--stated that 42 million doses of vaccines were distributed in 1962 and that, on the basis of a limited number of studies and preliminary reports, it was

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[1]Effective June 24, 1970, the National Communicable Disease Center became known as the Center for Disease Control.

believed that the efficacy of the vaccines was 20 to 25 percent at best.

The report concluded that widespread use of influenza vaccines for general population groups could not be justified but that high-risk groups should continue to use the vaccines annually. High-risk groups, at that time, were defined as pregnant women, the chronically ill, and older persons.

Another report published in 1969 by officials of the National Communicable Disease Center stated that the results of studies indicated that influenza vaccines at standard dosage levels had little, if any, effectiveness and that even very large doses of the vaccines did not approach the high degrees of effectiveness which had been achieved with other virus vaccines. The report concluded that attention should be directed toward finding a more effective means of protection against influenza.

A study, published in 1969, of the effectiveness of influenza virus vaccines by officials of the University of Wisconsin Medical School and of the National Communicable Disease Center concluded that inoculation clearly appeared to have no protective or modifying effect on the incidence of illness.

The Director of DBS, in a report published in 1969, also questioned whether the use of influenza virus vaccines had any detectable effect on the influenza epidemics which occurred in 1957 and 1968. The Director pointed out that in August 1968 virologists generally agreed that a significant change had occurred in one particular virus strain and that an epidemic was clearly predictable because available vaccines would provide only limited, if any, protection.

Although all the vaccines which were manufactured to combat the 1968 epidemic were not used, the Director stated that one of the problems in the face of any epidemic was the availability of the vaccines. He stated also that persons who really did not need vaccines received them while others in high-risk groups did not receive them.

Recommendations of the Public
Health Service Advisory Committee

The Public Health Service Advisory Committee on Immunization Practices made the following recommendation with regard to the use of influenza virus vaccines during the 1971-72 influenza season.

> "Annual vaccination is recommended for persons who have chronic debilitating conditions: 1) congenital and rheumatic heart disease, especially mitral stenosis; 2) cardiovascular disorders, such as arteriosclerotic and hypertensive heart disease, particularly with evidence of cardiac insufficiency; 3) chronic bronchopulmonary diseases, such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, emphysema, and advanced tuberculosis; 4) diabetes mellitus and other chronic metabolic disorders."

The committee also stated that:

> "Although the value of routinely immunizing all older age persons is less clear, those patients who have incipient or potentially chronic disease, particularly affecting cardiovascular and bronchopulmonary systems, should also be considered for annual immunization."

The committee did not recommend the vaccines for healthy adults and children.

The committee stated that control of epidemic influenza in the general population was not possible through routine vaccinations because influenza vaccines had been variably effective and had offered rather brief periods of protection.

Use of vaccines in Federal agencies

We examined into programs of influenza inoculation at selected Federal agencies to determine their compliance with the recommendations of the Public Health Service Advisory Committee on Immunization Practices. We undertook

this examination because of the conflicting information on the relative effectiveness of the vaccines and because of the problems with their availability, cited by the Director of DBS, which could be caused by not following the recommendations of the advisory committee.

Under the United States Code (5 U.S.C. 7901), health units of Federal agencies are operated either by the agencies or by a division of the Health Service and Mental Health Administration, HEW.

We selected eight Federal agencies in the Washington area that operated their own health units, to determine whether they had followed the advisory committee recommendations for the 1970-71 influenza season. The recommendations for the 1970-71 season were the same as those for the 1971-72 season.

The Health Service and Mental Health Administration had furnished the medical officers in charge of its health units with a copy of the advisory committee's recommendations and had advised them not to conduct mass influenza immunizations but to make the vaccines available on a request basis only. We noted that about 14 percent of the 140,000 employees served by the health units of the Health Service and Mental Health Administration received the influenza virus vaccines during the 1970-71 influenza season.

Our examination into the eight agencies which operated their own health units showed that (1) the specific recommendations of the advisory committee had not been made known to the employees in most cases and (2) a larger percentage of employees usually received the vaccines than did employees at agencies having health units operated by the Health Service and Mental Health Administration.

The information summarized below is from notices given to the employees of the eight agencies. Also shown for the eight agencies are the number and percentage of employees who received the influenza virus vaccines during the 1970-71 influenza season.

Department or agency	Recommendation to employees	Employees receiving vaccines	
		Number	Percent
National Aeronautics and Space Administration	Informed employees of vaccines' availability, and through other literature promoted inoculation	1,000	46
Federal Aviation Administration	Urged for all employees interested in this program of preventive medicine	1,407	40
Social Security Administration	Stated that the need for inoculation was a must for everyone having chronic diseases, those over 45 years of age, and pregnant women	5,000	33
Civil Service Commission	Urged all employees to take advantage of the immunization program, particularly persons having chronic diseases, persons over 65 years of age, pregnant women, and persons responsible for care of the sick	778	32
U.S. Army, Civilian Employees' Health Service	Stated that the vaccines were not recommended for healthy adults and children but were recommended for persons having chronic debilitating diseases and persons over 45 years of age having incipient or potential chronic diseases	15,142	26
Department of Agriculture	Advised employees that vaccines would be available to all and stated that persons over 45 years of age and persons having chronic illnesses had the greatest need	3,395	24
Postal Service	Informed employees only of vaccines' availability	500	24
Congress of the United States	Notice to employees was identical to the advisory committee recommendations	1,814	13

CONCLUSIONS

Our review of scientific studies indicated that the specific degree of effectiveness of influenza virus vaccines was questionable. In addition, in periods of epidemic, there may be a problem with the vaccines' unavailability to persons in high-risk groups for whom the vaccines are needed because, according to the Director of DBS, persons receive the vaccines who do not need them.

We found that several Federal agencies had notified their employees of the availability of the vaccines but had not made known the recommendations of the advisory committee regarding the types of persons that should be inoculated.

Considering the advisory committee's statement that control of epidemic influenza in the general population is not possible through routine vaccinations, we believe that action should be taken by the Secretary to fully inform Federal employees of the limitations and merits of receiving the vaccines and of the annual recommendations of the advisory committee.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that HEW fully inform Federal employees of the limitations and merits of receiving influenza virus vaccines and of the annual recommendations of the Public Health Service Advisory Committee on Immunization Practices.

CHAPTER 5

SCOPE OF REVIEW

Our review included interviews with DBS officials and an examination into (1) legislation and congressional hearings applicable to the regulation of biological products, (2) the manufacturers' protocols, DBS test results, DBS instructions, and DBS correspondence with manufacturers that related to the potency of influenza virus vaccines released for sale from 1966 to 1970, and (3) the recommendations of the Public Health Service regarding the use of the influenza virus vaccines. We also interviewed officials of selected agencies concerning their programs for the inoculation of Government employees against influenza.

Our review was made primarily at the offices of DBS in Bethesda, Maryland.

United States Senate

COMMITTEE ON
GOVERNMENT OPERATIONS
SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND
GOVERNMENT RESEARCH
(PURSUANT TO SEC. 7, S. RES. 31, 92D CONGRESS)
WASHINGTON, D.C. 20510

June 28, 1971

Honorable Elmer B. Staats
Comptroller General of the
United States
General Accounting Office Building
441 G Street
Washington, D.C. 20548

Dear Elmer:

The Public Health Service Act authorizes the Division of Biologics Standards of the National Institutes of Health to administer the regulation of biologic products. In the performance of this important function the Division must establish and maintain a high level of testing and inspection of production facilities for biologics produced for sale and shipment in interstate commerce. In addition, the Division has the power to take appropriate action to enforce restrictions on interstate shipments on unlicensed or mislabeled products.

During the past month, members of the staff of the Subcommittee on Executive Reorganization and Government Research and representatives of your office have discussed the regulatory activities of the Division. On the basis of these discussions and other Subcommittee information, it is clear that a review by your office of the regulatory responsibilities of the Division, particularly its activities involving influenza, adenovirus, combined influenza-adenovirus and pertussis vaccines is badly needed.

I therefore request that the General Accounting Office undertake such a study immediately and submit a full report to this Subcommittee at the earliest date possible.

In addition, I have attached a list of questions concerning the Isoniazid TB control drug and the Federal Government's procedures for assuring its safe use. I would like a separate report responding to these questions as well.

In view of the present working relationship between our staffs, further details involving this request can be arranged at the staff level.

Sincerely,

Abe Ribicoff
Chairman

Attachments [See GAO note.]

GAO note: The attachments have not been included in this report.

INDICATED USES OF BIOLOGIC PRODUCTS THAT ARE NOT GENERALLY RECOGNIZED AS BEING EFFECTIVE IN USE

1. Product A--Aids in the desensitization to common bacterial organisms present in the respiratory system.

2. Product B--Intended as a means of developing an immunity to pneumococci, streptococci, hemophilus influenzae, neisseria catarrhalis, and staphylococci.

3. Product C--Intended for treatment of mixed staphylococcus and streptococcus infections.

4. Product D--Intended as a means of developing an immunity to neisseria catarrhalis, klebsiella pneumoniae, diplococcus pneumoniae, streptococci, and staphylococci.

5. Product E--Intended as a means of developing an immunity to hemophilus influenzae, neisseria catarrhalis, streptococci, klebsiella pneumoniae, staphylococci, and pneumococci.

6. Product F--Intended as a means of developing an immunity to staphylococcus infections.

7. Product G--May be useful for increasing resistance to bacterial respiratory infections.

8. Product H--May be useful for certain infections and inflammations of the eye.

9. Product I--Used for active immunization against some of the bacteria that cause secondary infections associated with the common cold.

10. Product J--Used in the treatment of brucellosis.

11. Product K--Intended as a means of developing an immunity to upper respiratory tract infections due to strains of staphylococci and streptococci.

12. Product L--Intended as a means of developing an immunity to species of disease-producing bacteria that commonly cause respiratory tract infections.

13. Product M--Intended as a means of developing an immunity to disease-producing bacteria commonly associated with respiratory tract infections.

14. Product N--Used in the treatment of infections caused by staphylococcus aureus.

15. Product O--Used in the treatment of infections caused by staphylococcus aureus.

16. Product P--Used in the treatment of infections caused by staphylococcus aureus.

17. Product Q--For prevention of bacterial complication of the common cold and for treatment of chronic rhinitis and sinusitis.

18. Product R--Aids in the treatment of various forms of rheumatism, arthritis, myositis, fibrositis, chronic neuritis, and neuralgia.

19. Product S--Used in the treatment of subacute or chronic staphylococcal infections, such as acne, pustular dermatoses, furuncles, and blepharitis.

20. Product T--For prevention of secondary infections associated with respiratory infections.

21. Product U--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.

22. Product V--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.

23. Product W--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.

24. Product X--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.

25. Product Y--Used in the treatment of recurrent and chronic staphylococcal infections of the eyes, ears, and nose.

26. Product Z--Used in the treatment of recurrent and chronic staphylococcal infections of the skin.

27. Product AA--Aids in the treatment of inflammations produced by streptococci, staphylococci, colibacilli, and pneumococci.

28. Product BB--Intended for use when it is desired to attempt prophylaxis against staphylococci, neisseria catarrhalis, hemophilus influenzae, klebsiella pneumoniae, corynebacterium diphtheroides, diplococcus pneumoniae, and streptococci.

29. Product CC--Used for immunity and treatment of bacterial infections of the respiratory tract and accessory sinuses that are usually associated with acute colds.

30. Product DD--Used in the treatment of acute and chronic rheumatic conditions.

31. Product EE--Used for immunity and treatment of catarrhal infections of bacterial origin that involve respiratory passages and accessory sinuses.

32. Product FF--Used for immunity and treatment of respiratory infections of bacterial origin.

APPENDIX III

PRINCIPAL OFFICIALS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE RESPONSIBLE FOR THE ACTIVITIES DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
Elliot L. Richardson	June 1970	Present
Robert H. Finch	Jan. 1969	June 1970
Wilbur J. Cohen	Mar. 1968	Jan. 1969
John W. Gardner	Aug. 1965	Mar. 1968
ASSISTANT SECRETARY (HEALTH AND SCIENTIFIC AFFAIRS):		
Merlin K. DuVal	July 1971	Present
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov. 1965	Feb. 1969
DIRECTOR, NATIONAL INSTITUTES OF HEALTH:		
Robert Q. Marston	Sept. 1968	Present
James A. Shannon	Aug. 1955	Aug. 1968
DIRECTOR, DIVISION OF BIOLOGICS STANDARDS:		
Roderick Murray	Jan. 1956	Present